AMENDMENTS TO THE DRAWINGS

Applicants submit amended Figures 1, 3 and 4 to replace the Figures 1, 3 and 4 currently on file. Each drawing sheet submitted herewith is labeled "Replacement Sheet" in accordance with 37 C.F.R. § 1.121.

REMARKS

Claims 31-41 and 46-59 were pending in this application. Claims 31, 32, 39 and 57 are currently amended without any intent of disclaiming equivalents thereof. Claims 46 and 47 are withdrawn. New claims 60 and 61 are added. Accordingly, upon entry of this paper, claims 31-41 and 46-61 are pending and presented for consideration.

Claim Amendments

Claims 31, 32 and 57 are amended to correct informalities and for clarification. Claim 39 is amended to correct an inadvertent typographical error. Support for the amendment to claim 39 is found in the specification at least, for example, at page 9, line 27. Support for new claims 60 and 61 is found in the specification at least, for example, at page 6, lines 24-28.

Applicants submit that the amendments to the claims introduce no new matter.

Information Disclosure Statement

Applicants respectfully request that the Examiner consider the art cited in the PTO-1449 form submitted to the USPTO on October 21, 2005, and confirm this by initialing, signing and dating the PTO-1449 form. A copy of the PTO-1449 form and the Information Disclosure Statement submitted on October 21, 2005, together with a copy of the postcard date stamped October 21, 2005, by the USPTO indicating receipt of the PTO-1449 form are attached as Exhibit A. Applicants respectfully request that the Examiner return a copy of the initialed, signed and dated PTO-1449 form to the undersigned for completion of Applicants' files.

In addition, Applicants submit together with this response a supplemental Information Disclosure Statement and accompanying Form PTO-1449 listing publications in accordance with the provisions of 37 C.F.R. §§ 1.97 and 1.98 for consideration by the Examiner in connection with the examination of the present patent application.

Drawings

Applicants have amended Figures 1 and 3 to be consistent with the symbols used in the specification. Applicants have also amended Figure 4 to further distinguish the bars representing vWF:Ag and vWF:Ri Cof as requested by the Examiner.

Applicants submit that the amendments to the drawings introduce no new matter.

Amendments to Specification

Applicants have amended the specification to insert the generic terms of the trademarks ULTROSER® and SEPHAROSE® as requested by the Examiner. Applicants submit that the amendments to the specification introduce no new matter.

Claim Objections

The Examiner objected to claim 32 for not using the abbreviated form of the term "von-Willebrand factor." Applicants have amended claim 32 to replace "von-Willebrand factor" with the abbreviated form "vWF." Applicants respectfully request the objection to claim 32 be withdrawn.

The Examiner objected to claim 39 because, according to the Examiner, the phrase "the group" should be changed to "a group." Applicants respectfully submit that claim 39 recites a Markush group. As set forth in The Manual of Patent Examining Procedure (MPEP) § 2173.05(h)(I), a proper Markush group should recite members as being "selected from the group consisting of A, B and C." (*See*, MPEP, § 2173.05(h)(I), citing *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925)). Accordingly, Applicants respectfully submit that the language "an heterogeneous assay selected from the group consisting of" recited in claim 39 is proper. Therefore, Applicants respectfully request the objection to claim 39 be withdrawn.

The Examiner objected to claims 48 and 49 for not using the abbreviated form of the term "von-Willebrand disease" since the term has already been abbreviated in claim 31. Applicants have amended claim 31 to delete the abbreviated form of the term "von-Willebrand disease." The term "von-Willebrand disease" is now consistently recited in claims 31, 48 and 49. Accordingly, Applicants respectfully request the objection to claims 48 and 49 be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claim 53 is rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Specifically, the Examiner asserts that the terms "plastic" and "glass" recited in claim 53 are not supported by the specification. Applicants submit that support for "plastic" and "glass" is found in the specification at least on page 10, line

17. Accordingly, Applicants respectfully request the reject of claim 53 be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 31-41 and 48-59 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Specifically, the Examiner alleges that it is not clear whether or not the phrases "vWF-activity" and "vWF-antigen" cited in step (c) of independent claim 31 refer to "vWF-activity" recited in step (a) and "vWF-antigen" recited in step (b). Applicants have amended the step (c) of claim 31 to specifically recite "determining the ratio between vWF-activity detected under step (a) and vWF-antigen determined under step (b) for said sample." Accordingly, Applicants respectfully request the rejection of independent claim 31 and its dependent claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 103(a) over Favaloro et al. in view of Hoylaerts et al.

Claims 31-33, 35, 37-41, 48 and 49 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro *et al.* (Pathology, 1993, 25:152-158) in view of Hoylaerts *et al.* (Biochem. J., 1995, 386:453-463). Applicants respectfully traverse this rejection for the reasons enumerated below.

Even if the disclosures of Favaloro *et al.* and Hoylaerts *et al.* were properly combined, which Applicants respectfully submit they are not, such a combination would not teach Applicants' invention as claimed in claim 31. Claim 31 recites a method for detecting von-Willebrand disease by, *inter alia*, "detecting von-Willebrand factor (vWF) activity in a sample using a soluble form or a portion of glycoprotein 1b(α) (GPIb(α)) and ristocetin or a functionally equivalent substance." The teachings of the primary reference, Favaloro *et al.*, are deficient in at least one of the claimed elements. Applicants submit that Favaloro *et al.* teaches a method for detecting von-Willebrand disease based on a collagen binding assay (*see, e.g.*, Favaloro *et al.*, page 153, right column, and page 156, left column). Favaloro *et al.* does not teach or suggest a method for detecting von-Willebrand disease by detecting WF activity in a sample using a soluble form or a portion of GPIb(α) and ristocetin or a functionally equivalent substance.

Hoylaerts *et al.* does not correct the deficiency of Favaloro *et al.* In the Office Action, the Examiner asserts that "Hoylaerts et al. teaches a method of detecting vWF activity in a sample (human plasma) using a soluble form or a portion of glycoprotein 1b(α) (GP1b(α)) and ristocetin (p454, Purification of Gp1b, Purification of vWF, and Studies of Interaction between vWF and GP1b)" (*see*, the Office Action, page 9). Applicants respectfully disagree with the Examiner's reading of Hoylaerts *et al.* Hoylaerts *et al.* is directed to understanding how ristocetin mediates the binding of vWF to the GP1b complex (*see, e.g.*, Hoylaerts *et al.*, page 454, left column, first paragraph). Specifically, Hoylaerts *et al.* teaches an Elisa method for detecting the interaction between vWF and the GP1b protein complex in the presence of ristocetin. As set forth on page 454, in the paragraph under "Purification of Gp1b," Hoylaerts *et al.* teaches use of a GP1b protein complex containing both chains and the associated GPIX in its method. Therefore, contrary to the Examiner's assertion, Hoylaerts *et al.* does not teach or suggest use of a soluble form or a portion of GP1b(α) as required in claim 31. Indeed, it is critical to use a structurally intact GP1b protein complex in Hoylaerts's method since Hoylaerts is directed to understanding the mechanism of how ristocetin promotes the interaction between vWF and the GP1b protein complex. Therefore, the combination of Favaloro *et al.* and Hoylaerts *et al.*, even if proper, does not provide the required soluble form or portion of GP1b(α) in a vWF binding test as claimed by Applicants. Accordingly, Applicants submit Favaloro *et al.* and Hoylaerts *et al.* is an improper combination under 35 U.S.C. § 103 at least because neither teaches or suggests detecting vWF activity using a soluble form or a portion of GP1b(α) as required in claim 31.

In view of the foregoing, Applicants respectfully submit that claim 31 and any claims dependent therefrom are novel and unobvious over Favaloro *et al.* in view of Hoylaerts *et al.* Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 31 and dependent claims 32, 33, 35, 37-41, 48 and 49.

Rejections Under 35 U.S.C. § 103(a) over Favaloro et al. in view of Hoylaerts et al. and in further view of Handin

Claims 34, 36, 50-53 and 56-59 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro *et al.* in view of Hoylaerts *et al.* and in further view of Handin (U.S. Patent No. 5,321,127). Applicants traverse the rejection for the reasons enumerated below.

As discussed above, claim 31 and any claims dependent therefrom including claims 34, 36, 50-53 and 56-59 are novel and unobvious over Favaloro *et al.* in view of Hoylaerts *et al.*, alone or in combination. Handin does not correct the deficiency of Favaloro *et al.* or Hoylaerts *et al.* Applicants submit that Handin teaches a specific fragment derived from Gp1b(α) (rGp1bαQ221-L318) that inhibits the ristocetin-dependent binding of vWF to platelets and the spontaneous binding of vWF to collagen (*see, e.g.*, Handin, column 3, lines 16-20). Handin is silent with respect to methods for disease detection of any sort, in particular, whether the GP1b(α)-derived fragment taught by Handin would be useful to detect vWF activity in the presence of ristocetin or a functionally equivalent substance in order to detect von-Willebrand disease in a sample. Handin also does not provide an expectation of success that a soluble form or a portion of GP1b(α) can be used for detecting von-Willebrand disease. Therefore, Applicants submit claim 31 and any claims dependent therefrom are novel and unobvious over Favaloro *et al.*, Hoylaerts *et al.*, and Handin, either alone or in combination. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 34, 36, 50-53 and 56-59.

Rejections Under 35 U.S.C. § 103(a) over Favaloro et al. in view of any combinations of Hoylaerts et al. and Handin and in further view of Elings et al.

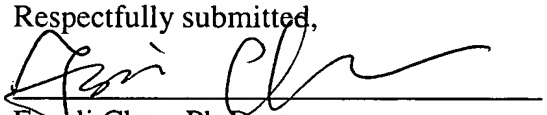
Claim 54 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro *et al.* in view of Hoylaerts *et al.* and Handin, and in further view of Elings *et al.* (U.S. Patent No. 4,537,861). Claim 54 also stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro *et al.* in view of Hoylaerts *et al.*, and in further view of Elings *et al.* Applicants traverse the rejections for the reasons enumerated below.

As discussed above, claim 31 and any claims dependent therefrom including claim 54 are novel and unobvious over Favaloro *et al.*, Hoylaerts *et al.* and Handin, alone or in combination. Elings *et al.* does not correct the deficiency of Favaloro *et al.*, Hoylaerts *et al.* or Handin discussed above. Applicants submit that Elings *et al.* teaches an immunoassay permitting measurement of the desired signal at a very low concentration (*see, e.g.*, Elings *et al.*, column 5, lines 42-48). Elings *et al.* does not teach or suggest use of a soluble form or a portion of GP1b(α) in a vWF binding test in a method to detect von-Willebrand disease in a sample. Therefore, Applicants submit claim 31 and any claims dependent therefrom are novel and unobvious over Favaloro *et al.,* Hoylaerts *et al.*, Hardin and Elings *et al.*, either alone or in any combinations. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claim 54.

CONCLUSION

Applicants believe that all of the art of record has been overcome and claims 31-41 and 46-61 are in condition for allowance. The Examiner is invited to telephone the undersigned agent to discuss any remaining issues. Early and favorable actions are respectfully solicited.

Respectfully submitted,



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